Newton in view of Sorenson and Mullis et al. (U.S. Patent No. 4,965,188; hereafter "Mullis"). Claim 8 is indicated to be allowable if rewritten in independent form.

Rejections under 35 U.S.C. §112, second paragraph

Claims 2-5 are rejected for indefiniteness, with the Examiner stating, "[I]t is unclear what is meant by the language 'different ranges of specificity' in claim 2." Applicants traverse this rejection. As noted in the previous replies, the definition of "range of specificity" is given on page 6 of the specification. This definition reads:

> By "range of specificity" is meant the range of nucleic acid template:PCR primer ratios at which template sequences differing by at least one nucleotide may be discriminated by assaying for the presence of detectable PCR amplification product formation.

Applicants note that "specificity" in this context means the ability to amplify a target sequence preferentially over non-target sequences. This preferential amplification occurs not just at one concentration of primer and target but over a range of concentrations of primer and target. This range is thus referred to as the "range of specificity." In general, the present invention employs two sets of primers that are specific for the target sequence over different ranges of specificity. As illustrated in Figure 4, one set of primers may have a range of specificity of 0.001 to 1 over which that set of primers preferentially amplifies the target sequence over non-target sequences. A second set of primers may have a range of specificity of 0.02 to 10 over which the second set of primers preferentially amplifies the target sequence over non-target sequences. Since the ranges of specificity of these two illustrative sets of primers are not the same, the two sets of primers are said to have "different ranges of specificity." Applicants further note that this

language is consistent with the dictionary meanings for "different," "range," and "specificity." Furthermore, Applicants assert that one skilled in the art would readily understand the meanings of "range of specificity" and "different ranges of specificity" from the definitions provided in the specification.

The Office has further stated that "it is unclear what is meant by the language '3000-fold range of specificity'. Does it mean that the specificity is within the range of 3000 nucleotides sequence long[?]" Applicants also traverse this rejection. As noted in the previous replies, 3000-fold refers to the extent of the range of specificity, i.e., the modifier "3000-fold" means that the highest concentration at which a target sequence is preferentially amplified is 3000 times the lowest concentration at which the target sequence is preferentially amplified. For example, the 0.001 to 1 range described above is a 3000-fold range. In reply to the Examiner's question, Applicants note that the term 3000-fold does not refer to a number of nucleotides but rather to the concentrations of the target DNA and the PCR primers. One skilled in the art would readily understand the meaning of "3000-fold range of specificity" based on the specification, especially in view of Figures 3 and 4, which graphically illustrate the meaning of the term.

The Office also states that the meaning supplied by Applicants in the previous reply is not recited in the claim language, and thus, the rejection was maintained. Applicants note that M.P.E.P. § 2173.05(a) states that "[d]uring patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification" (citations omitted, emphasis added). Since the meaning of "3000-fold range of specificity" is evident to one skilled in the art from the specification, the term is

definite and needs no further elaboration in the claims. In view of the foregoing, the rejection of claims 2-5 for indefiniteness should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 6, 7, 9, 12, and 14-20 stand rejected for obviousness over Newton in view of Sorenson. Applicants traverse this rejection.

Claims 1 and 15, the independent claims rejected, are directed to a method and a kit for determining whether a nucleic acid sequence comprises a particular allele of a polymorphic sequence. Each of these claims requires first and second pairs of primers, characterized as follows:

> (i) one of said first pair of PCR primers is (a) complementary at its 3'-terminal nucleotide to a first allele of said polymorphic sequence ...
>
> (ii) one of said second pair of PCR primers is (a) complementary at its 3'-terminal nucleotide to said first allele of said polymorphic sequence ...

Thus, claims 1 and 15 require two primers (one from each set) that have the same nucleotide at their 3' termini. Both sets of primers are capable of amplifying the same allele.

M.P.E.P. § 2142 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

This standard has not been met in the present case.

The combination of Newton and Sorenson does not teach or suggest all of the limitations of claim 1 or claim 15. Neither reference teaches or suggests the detection of an allele by employing PCR using two different sets of primers with one primer in each set having an identical 3' terminal nucleotide, both sets of primers binding to the same allele. The Office acknowledges the deficiencies of Newton by stating that it does "not disclose more than one pair of PCR primers are used in the method." Regarding Sorenson, the Office states that the method of Sorenson employs four primer pairs that "are unique with respect to each other and differ only at the 3' nucleotide ... (as recited in the limitations of claims 1-2 and 14)." While Sorenson does teach the use of four sets of primers, each set binds to a different allele, and thus no two sets of primers bind to the same allele as required by claims 1 and 15.

In addition, contrary to the Office's assertion, instant claims 1-2 and 14 do not recite the use of primers that have different 3'-terminal nucleotides for the amplification of the same gene. This fundamental difference between Sorenson and the present invention has been discussed above and in previous replies, and has been illustrated in the figure submitted with the previous reply. The features of the present invention are illustrated in that figure under the heading "Claimed invention." In that example, a primer from the first pair and a primer from the second pair have a T at their 3' ends, each of which is complementary to the A in the first allele (boxed in the figure). In contrast, Sorenson teaches the use of "four primers [that] are unique with respect to each other and differ ... at the 3' nucleotide which is complementary to the wild type

nucleotide or to one of the three possible mutations which can occur at this known position." (Col. 2, ll. 30-34; Emphasis added). The method of Sorenson is illustrated in the Sorenson patent at Figure 1B and is represented in the previously submitted figure under the heading "Sorenson reference." In Figure 1B and Applicants' representation, four primers are present, and each primer has a different 3' terminal nucleotide. Accordingly, only one of these primers can possibly have a 3' nucleotide that is complementary to a "first allele." Sorenson therefore does not teach or suggest the use of two primers that are each complementary to a first allele at their 3' ends as required by independent claims 1 and 15.

Moreover, the Office's statement that "Sorenson further suggests that some mismatches 3-6 nucleotides back [may be] made and the 3' terminal nucleotide must remain the same..." is irrelevant to the patentability of the instant claims. When Sorenson states that the 3' terminal nucleotide must remain the same, the reference refers to the fact that changes, e.g., insertions, deletions, or mismatches, may be made in an individual primer so long as the 3' terminal nucleotide is not altered. The alteration of a 3' terminal nucleotide of one of the Sorenson primers would render their method inoperable since the method requires four primers having different 3' terminal nucleotides. The teachings of Sorenson, therefore, do not remedy the deficiencies of Newton. Thus, the combination of the prior art cannot render Applicants' claims obvious since, even in combination, these references do not teach or suggest all of the limitations of claim 1 or claim 15.

Furthermore, regarding the motivation to modify Newton, the Office states that "Newton et al. indicate that the method can be used in detecting the presence or absence of more than one suspected variant nucleotide in the same sample... This teachings would have motivated one of ordinary skill in the art ... to apply more than one pair of PCR primers for the detection." While Newton may provide motivation to employ two sets of primers to detect more than one suspected variant nucleotide, such motivation is irrelevant to the patentability of the instant claims. As stated above, the instant claims are directed to a method of detecting an allele using two sets of primers that are both capable of amplifying the same allele. Thus, any motivation stemming from using multiple primers to detect multiple alleles is misplaced, i.e., even if Newton was modified as suggested by the Office, it would still not teach or suggest the limitations of the instant claims.

The Office provides further asserted motivation to modify Newton, stating that Sorenson teaches that "where the mutation may exist at one or two locations, eight pair[s] of oligonucleotide primers may be used..." As with the motivation provided by the Office for Newton alone, this motivation provided by the teaching of Sorenson, even if true, is irrelevant to patentability. As stated above, any modification of Newton based on the use of more than one pair of primers to detect more than one allele does not yield the instant claims.

For all of the above reasons, Applicants submit that the Office has failed to provide a prima facie case of obviousness for claims 1, 6, 7, 9, 12, or 14-20. This rejection should be withdrawn.

Claims 10 and 13 also stand rejected as being obvious over Newton and Sorenson in view of Mullis. This rejection is respectfully traversed. Claim 10, from which claim 13 depends, is directed to the method of claim 1 with the additional limitation that certain of the primers include a unique hybridization tag. As stated above, the combination of Newton and Sorenson does not teach or suggest the method of claim 1, and Mullis does not remedy this deficiency. Therefore, the combination of Newton and Sorenson with Mullis fails to teach or suggest the method of claim 10 or 13. This rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance and such action is requested. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

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